REMARKS

Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 are pending in this application. Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 were variously rejected under 35 U.S.C. § 112, first paragraph. Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 were rejected under 35 U.S.C. § 112, second paragraph. Claims 41, 42, 44-46, 48, 49, 65 and 68-73 were rejected under 35 U.S.C. § 103.

Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Written Description

Claims 56, 57, 62, 63, 66 and 70-73 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this ground for rejection.

In satisfying the written description requirement, an Applicant must convey with reasonable clarity to those skilled in the art that he or she was in possession of the claimed invention at the time of filing. However, "the subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement" (M.P.E.P. § 2163.02).

With regard to claim 66, the Examiner continues to assert that "the specification does not contemplate administering RPE that are allogeneic to the host." Office Action, page 3. Applicants again respectfully disagree. Originally filed claims 1 and 2 recite a method that involves "administering RPE cells." Originally filed claim 7 depends from claim 1 or claim 2 and recites that the "administering is by transplantation." Originally filed claim 12 depends from claim 7 and recites that the "transplantation is by allograft." Thus, the original claims describe an allograft transplantation of RPE cells, *i.e.*, administering RPE cells which are allogeneic to the host. Contrary to the Examiner's assertion, Applicants respectfully submit that the specification as filed conveys to one skilled in the art methods involving administering RPE cells that are allogeneic to the recipient.

Applicants respectfully submit that pending claims 56, 62 and 72 are described in the specification as filed and do not contain new matter. Original claims 16 and 21 describe a pharmaceutical composition and an compartmentalized kit, respectively, which include RPE cells and cells that produce a therapeutic molecule (*i.e.*, non-RPE cells). As with claims 56, 62 and 72, claims 16 and 21 do not recite an allogeneic relationship between the RPE and the non-RPE cells. Thus, the previous deletion of "allogeneic" from the claims 56, 62 and 72 does not constitute adding new matter.

The specification describes compositions comprising RPE cells and non-RPE cells which produce therapeutic proteins or biologically active molecules for use in treating diseases including metabolic diseases such as diabetes. See, for example, page 5, line 23, to page 6, line 2; original claims 4 and 13. As noted by the Examiner, the specification also describes that the non-RPE cells may be insulin producing β-cells (page 4, lines 33-34) or pancreatic islet of Langerhans cells (original claim 22). Applicants respectfully submit that such a description in the specification conveys to one skilled in the art that the non-RPE cells of the claimed invention includes "insulin producing cells."

In view of the foregoing, Applicants respectfully submit that the written description requirement has been met.

Enablement

Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 were rejected under 35 U.S.C. §112, first paragraph, for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

Applicants maintain that the specification in its entirety provides sufficient guidance to teach one of skill in the art how to make and use the invention for facilitating survival of an allograft as claimed. Applicants respectfully traverse the Examiner's assertion that insufficient guidance is provided and respectfully submit that a *prima facie* case of non-enablement has not been established.

The claimed invention is directed to a method for facilitating survival of an allogeneic graft of non-RPE cells in a mammal through administering RPE cells and a population of non-RPE cells to a site in a mammal, where the non-RPE cells are allogeneic to the mammal. The RPE cells secrete Fas L and are administered in an amount effective to create localized immunosuppression at the site thereby increasing survival time of the allogeneic graft of the population of non-RPE cells in the mammal. The claimed invention is also directed to a pharmaceutical composition, a compartmentalized kit and an article of manufacture comprising RPE cells and insulin-producing cells.

The Examiner states that the specification enables administration of RPE cells and allogeneic non-RPE cells to a mammal but asserts that it does not enable increasing survival of the non-RPE cells in the mammal or producing a therapeutic protein/biologically active molecule by administering the non-RPE cells. Office Action, paragraph bridging pages 3 and 4.

Although in this rejection the Examiner apparently doubts the truth or accuracy of the specification, acceptable evidence or reasoning to support this position has not been provided. Applicants respectfully submit that the state of the art described and the art cited by the Examiner does not adequately support the lack of enablement contention.

Applicants submit that producing a therapeutic protein/biologically active molecule by administering non-RPE cells to a mammal was well known in the art at the time of filing. The Examiner acknowledges this and cites three references which support this position, Sigalla, Weber and Fraser. Office Action, paragraph bridging pages 4 and 5. Sigalla describes restoration of normoglycemia in syngeneic, diabetic mice upon transplantation of pancreatic islet cells. Weber describe restoration of normoglycemia in immunodeficient, diabetic mice upon transplantation of pancreatic islet cells. Fraser describes 90 day viability of implanted pancreatic islets encapsulated within a biocompatible membranes to avoid rejection.

In addition to these references, Cherksey (U.S. Pat. No. 5,618,531, of record) teaches that administration of dopamine secreting adrenal chromaffin cells to a brain with a lesion in the dopamine system reduces Parkinson-like symptoms in a standard animal model for Parkinson's disease. See, for example, Cherksey, Example IV. Thus, Cherksey teaches obtaining therapeutic levels of a biological molecule produced by non-RPE cells protected within the brain, an immune privileged site. In addition, both Cherksey and Ye (of record) indicate that transplantation of RPE cells into a mammal was known in the art at the time of filing.

In the specification and in the response to the Office action submitted September 30, 2002, Applicants point out that Selawry (in *Cell Transplantation* and in U.S. Pat. No. 5,725,854) demonstrates that transplantation of Sertoli cells together with allogeneic pancreatic islet cells in the renal subcapsular space of diabetic rats results in some of the animals becoming normoglycemic. As described in the specification and in Selawry, the Sertoli cells create an immunologically privileged site for the co-administered cells. Thus, Selawry teaches

transplantation of non-RPE cells within an immune privileged site where the non-RPE cells produced therapeutic levels of a biological molecule.

In stating that this argument was not persuasive, the Examiner asserts that the "specification does not provide adequate correlation between Sertoli cells and RPE such that similar results could be obtained. It cannot be determined if Sertoli cells and RPE create an immune privileged site by the same means, if both Sertoli cells and RPE secrete FasL." Office Action, page 8. Applicants respectfully disagree with this assertion.

At page 3, lines 11-23, the specification describes the Selawry studies with Sertoli cells and that Sertoli cells constitutively express FasL. Streilein (1995, of record) also describes that Sertoli cells constitutively express FasL. See, for example, Streilein, page 1158, center column. Applicants respectfully submit that correlation between immune privilege and FasL secretion of Sertoli cells and of RPE cells is provided by the specification. Thus, the Selawry references of record support the claimed invention.

The Examiner continues to assert that "RPE were known to provide "immune privilege" (Ye of record, 1993 ... ." Office Action, page 5. Applicants again respectfully disagree with this assertion and characterization of the teachings of Ye for the reasons stated in the response to the Office Action submitted September 30, 2002. Contrary to teaching that RPE cells provide immune privilege, Ye states that the "successful allotransplantation [of RPE cells] raises the possibility that the subretinal space of the rabbit might enjoy some degree of immunologic privilege." Ye, abstract, last line. Thus, according to Ye, the site of administration, the subretinal space, allows for the survival of the allotransplanted RPE cells. The other cited passages of Ye do not appear to be on point with the Examiner's assertion and so they are not addressed here.

At several places in the rejection the Examiner refers to "the structure of a site resulting from administering RPE and allogeneic non-RPE to a mammal" and that neither the specification nor the art teach the "structure" of such a site. The claimed invention relates to creating

localized immunosuppression at the site of RPE and non-RPE administration. Neither the claims nor the specification discuss a requirement for a particular structure of the site. Applicants respectfully submit that the Examiner's discussion regarding the structure of the site resulting from administration is not pertinent to the claimed invention.

Thus, contrary to the Examiner's assertion that knowledge in the art does not support the activity of non-RPE protected within an immune privileged site, non-RPE cells, as described in the present invention, have been successfully transplanted together with cells that create an immune privileged site such that the transplanted cells avoid rejection and produce a therapeutic amount of a biologically active molecule in the host. Although the Examiner refers to "unpredictability in the art," Applicants respectfully submit that the cited references and arguments put forth by the Examiner do not adequately support the lack of enablement rejection of the claimed invention.

Applicants again respectfully submit that the standard for determining an enabling disclosure is not limited to what is described in a particular example of the specification. In fact, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)*; M.P.E.P. § 2164.02.

Applicants submit that a *prima facie* case of non-enablement has not been established and that the specification provides sufficient guidance for one skilled in the art to make and use the invention as claimed.

Accordingly, the pending claims are in compliance with the enablement requirements.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

With regard to claim 65, the Examiner states that it "appears that the preamble is intended to increase the survival time of all allogeneic cells that are administered to the host." The Examiner then suggests that the language be changed to "increasing survival of a population of non-RPE cells." Office Action, page 9.

Applicants respectfully disagree with this assessment of the claim and submit that the pending claim language is not indefinite. The preamble of claim 65 states that the method is for "facilitating survival of an allogeneic graft of a population of non-RPE cells in a mammal." Thus, the claim is clearly referring to "an allogeneic graft of a population of non-RPE cells" and not to all allogeneic cells administered. Although Applicants appreciate the Examiner suggestion of different claim language, Applicants respectfully submit that the suggested language would not particularly point out the claimed invention since it would not distinguish the graft of allogeneic non-RPE cells from endogenous, non-RPE cells pre-existing in the recipient mammal.

With regard to the suggestion that the preamble language "facilitating survival" be changed to "increasing survival" to match the body of the claim, Applicants respectfully submit that the use of "facilitating survival" in the preamble and of "increasing survival time" in the body of the claim does not render the claim indefinite. The claimed invention relates to the discovery that RPE cells secrete large quantities of FasL and thus can create a localized immunologically privileged site at the site of transplantation. The administering of a population of non-RPE cells to the site with the RPE cells increases the survival time of the non-RPE cells because of the localized immunosuppressive environment created by the RPE cells. Thus, claim

65 provides a method for facilitating survival of an allogeneic graft of a population of non-RPE cells through the presence of the RPE cells which create the immune privileged site. As stated in the body of the claim, the effectiveness of the method is measured with an increase in the survival time of the population of non-RPE cells in the mammal.

The Examiner also states that, with claim 65, "it is unclear to what the survival time of the population of non-RPE cells is being compared" and asks "[i]s the survival time greater in the mammal than *in vitro*? greater in the mammal using RPE as compared to administering the non-RPE cells alone?" Office Action, page 9.

As is clear from the specification, the claimed invention is directed to the use of RPE cells to create local immunosuppression to allow increased survival of co-transplanted, non-RPE cells as compared to survival of the non-RPE cells transplanted without the RPE cells. See, for example, pages 4 and 7. "The method of the present invention may be used for enhancing the outcome of tissue transplants, by providing localized immunosuppression. That is, RPE cells may be used to facilitate transplant survival and graft function of the cells being transplanted." "The co-administering of RPE cells has the advantage in that the RPE cells create an immunologically privileged site thereby increasing the survival time of the co-administered cells."

Thus, Applicants believe that the claims are sufficiently definite when considered in view of the specification and the understanding of those of skill in the art.

The Examiner lists claims 56, 57, 62, 63 and 70-73 in this rejection. Since the Examiner's comments do not appear to relate to these claims, their rejection has not been addressed herein. Claim 55 was previously cancelled.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. §103

Claims 42, 42, 44-46, 48, 49, 65 and 68-73 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Cherksey (U.S. Patent 5,618,531). Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143.

Applicants respectfully submit that the cited reference, Cherksey, does not support a *prima facie* case of obviousness with regard to the claimed invention.

As presented in the specification, the present invention is based on the discovery that retinal pigment epithelial (RPE) cells secrete an immunosuppressive cytokine, Fas L, and can thereby produce a localized immunosuppressive environment at the site of RPE cell implantation. The claimed invention is directed to a method for facilitating survival of an allogeneic graft of non-RPE cells in a mammal through administering RPE cells and a population of non-RPE cells to a site in a mammal, wherein the non-RPE cells are allogeneic to the mammal. In the method, the RPE cells secrete Fas L and are administered in an amount effective to create localized immunosuppression at the site thereby increasing survival time of the allogeneic graft of the population of non-RPE cells.

The Examiner states that Cherksey does not teach co-administering RPE and non-RPE cells but that "Cherksey suggests transplanting a matrix having both RPE and glial cells attached

(column 9, line 2)." Office Action, page 10. Applicants respectfully disagree with this interpretation of Cherksey as a basis for the rejection.

Cherksey describes "co-culture of neural or paraneural cells with glial cells, their co-incubation with a support matrix, followed by implantation of the support matrix carrying both cell types" (column 9, lines 3-6). As noted in Cherksey (column 8, line 65 through column 9, line 2), transplantation of glial cells into the brain was known in the art. Thus, Cherksey describes implantation of a support matrix carrying cell types, neural or paraneural cells and glial cells, which are known to survive implantation into the brain, a known immune privileged site.[1] Cherksey must be considered in its entirety, including that the cells in Cherksey are transplanted into a pre-existing immune privileged site. Cherksey does not teach or suggest the use of neural or paraneural cells to create an immune privileged site, much less the use of RPE cells to create local immunosuppression.

Cherksey is silent with regard to creation of an immune privileged site for the co-administered glial cells and with regard to the ability of RPE to create an immune privileged site through secretion of FasL. The Examiner states that "RPE cells inherently secrete FasL" and that "Cherksey need not teach the inherent feature of the RPE cells as claimed." Office Action, page 11. However, without recognition that RPE cells secrete FasL to create localized immunosuppression, there is no motivation for one to modify the teaching of Cherksey and specifically select RPE cells from the various neural and paraneural cells taught in Cherksey for use in the presently claimed invention, *i.e.*, a method in which RPE cells are used to create localized immunosuppression.

Further, the teachings of Cherksey would provide no expectation of success for the claimed invention since there is no teaching or suggestion of transplantation outside of a pre-existing immune privileged site. Nor is there any teaching or suggestion that neural or paraneural cells in general can be used to create an immune privileged site.

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[1] See Streilein (1995, of record) for a list of immune privilege sites existing in the body.

Accordingly, Cherksey does not support *prima facie* obviousness with regard to the claimed invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSIONS

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000500. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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